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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/667,216
Filing Date: September 19, 2003
Appellant(s): MOUSA, SHAKER A.

Jack P. Friedman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 07 Jul 2009 appealing from the Office action mailed 27 Oct 2008.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments

The appellant's statement of the status of amendments contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(a) Grounds of Rejection Withdrawn

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner.

Rejection of claims 1, 2, 5, 6, 43, 49-54, 56-59, 61-63 and 91-94 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been **withdrawn**, as Appellant's remarks have been fully considered and are persuasive that the specification provides adequate description of the structural features necessary for one of skill in the art to visualize or recognize the identity of the members of the genus having the recited functional properties.

Rejection of claims 49-54 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been **withdrawn**, as Appellant's remarks have been fully considered and are persuasive that one of skill in the art is able to visualize or recognize the identity of the members of the genus recited in Claim 49: non-heparin anticoagulant; Claim 50: anti-Xa compounds, anti-IIa compounds, anti-tissue factor compounds, anti-VIIa compounds; Claim 51: a non-heparin angiogenic inhibitor; Claim 52: integrin inhibitory compounds, fibroblast growth factor inhibitors, fibroblast growth factor receptor inhibitors, vascular endothelial growth factor inhibitors; Claim 53: a cytotoxic or chemotherapeutic agent; Claim 54: non-classic alkylators, antitumor antibiotics, microtubule agents.

Rejection of claims 54 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been **withdrawn**, as Appellant's remarks have been fully considered and are persuasive that one of skill in the art is able to visualize or recognize the identity of the members of the genuses "platinum

complexes" and "substituted urea" recited in claim 54 in the context of the instant invention.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

4,727,063	**Naggi et al.**	**2-1988**
6,075,013	**Weitz et al.**	**6-2000**
5,280,016	**Conrad et al.**	**1-1994**
6,461,665	**Scholander**	**10-2002**

Definition of Activated Partial Thromboplastin Time, Massachusetts General Hospital Pathology Service, http://www.massgeneral.org, accessed online on 20 Oct 2008.

Definition of Heparin Antifactor Xa Assay, Massachusetts General Hospital Pathology Service, http://www.massgeneral.org, accessed online on 20 Oct 2008.

Kerbel et al. Cancer and Metastasis Reviews, 20 (2001), pp. 79-86.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

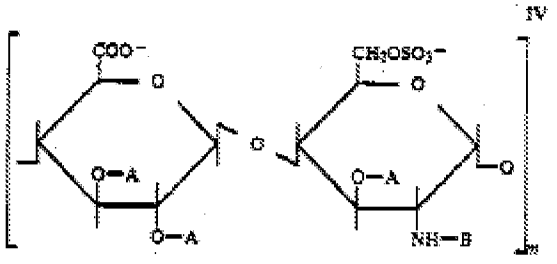
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 1, 2, 5, 6, 43, 91-94 are rejected under 35 U.S.C. 102(b) as being anticipated by Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record). Definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service (Massachusetts General Hospital Pathology Service, of record) provide evidence regarding the Activated Partial Thromboplastin Time and Anti-Xa disclosed by Naggi et al.

Naggi et al. discloses the structure as formula IV,



, wherein m is an integer from 4 to 15, A is H or SO_3^-, and B is SO_3^-or $COCH_3$ (column 6, lines 1-19). Naggi et al. discloses a broader disclosure of depolymerized and supersulfated heparin having a molecular weight between 2000 and 9000 and a sulfation degree of at least 2.5 and the process for its preparation comprising sulfating heparin (abstract). Naggi et al. discloses a preferred sulfation degree of from 3.0±0.1 to 3.3±0.1 (column 6, lines 54-57). Naggi et al. discloses a preferred embodiment of depolymerized and supersulfated heparin wherein the molecular weight is 3000-5000 and the sulfation degree is 2.6 (example 12 at

column 12, lines 1-30), or a heparin fraction wherein 52% of the primary and secondary hydroxyl groups are substituted by O-sulfate esters, meeting limitations of instant claim 1, 2, 5, 6, 91-93. The term “sulfate to carboxylate ratio of about 5:1" in instant claim 91 broadens the ratio without guidance as to the range encompassed by the term "about", and the disclosed sulfation degree of 2.6, or ratio of sulfate to carboxylate of 2.6:1, is interpreted to be about 5:1 because it is the same order of magnitude. Naggi et al. discloses the compound in the form of a pharmaceutical composition (column 10, lines 55-57), or a composition comprising about 100% of the depolymerized and supersulfated heparin and about 0% of heparin, low molecular weight heparin, chondroitin sulfates, dermatan sulfates, heparan sulfates, heparin derivatives, or combinations thereof, meeting the limitations of instant claim 43. Naggi et al. discloses the heparin treated with sulfuric acid and chlorosulfonic acid, a strong oxidizing agent, to depolymerize and super-sulfate heparin (example 12 at column 12, lines 1-30), which necessarily encompasses the reaction sequence comprising the steps of oxidizing said heparin in order to depolymerize said heparin and then performing sulfate substitution at oxygen bonds within repeating units of said oxidized depolymerized heparin to produce the super-sulfated heparin of formula IV, meeting the instant limitations of instant claim 94.

Naggi et al. discloses the reduction of the anticoagulation reduction characteristic with regards to the activated partial thromboplastin time (APTT) (column 9, lines 7-11 and 47-60), meeting the limitations of instant claims 5 and 93. Definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts

General Hospital Pathology Service show that determination of levels of anticoagulation are known in the art to be acceptably measured in terms of units/mL (Heparin Antifactor Xa Assay, page 2, sections **Reference Interval** and **Use**) in addition to times. The definition of Activated Partial Thromboplastin Time from Massachusetts General Hospital Pathology Service shows the Heparin Antifactor Xa Assay is an equivalent assay to the measurement of Activated Partial Thromboplastin Time (Activated Partial Thromboplastin Time, parage 2, section **Limitations**.) The depolymerized and supersulfated heparin disclosed by Naggi et al. shows a reduction of the APTT or Anti-Xa as measured in terms of units/mL in table I (column 9, lines 50-65) for products AH-17 and AH-19, relative to the heparin D-212, the reduction being approximately 76.5% (0.05 U/ml / 0.212 U/ml) for the same dose (50 IU/kg), or a reduced prolongation of clotting time of human blood by at least 75% relative to the prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT).

Naggi et al. is silent as to an angiogenesis inhibition characteristic and the anticoagulant reduction characteristic in terms of a “percent inhibition of platelet clot strength," but does recite that the depolymerized and supersulfated heparin shows a weak anticoagulant activity (column 5, lines 41-45), providing evidence tending to show inherency when combined with said activity measured with regard to APTT and Anti-Xa.

Therefore it is apparent from what is disclosed that the functional characteristics recited in instant claims 2 and 6 are inherent in the compound disclosed by Naggi et al.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the Appellants to "prove that subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second column, first full paragraph).

Claim 1 recites the product-by-process, “wherein the super-sulfated oxidized heparin fraction has a chemical structure of a first oxidized heparin fraction after the first oxidized heparin fraction has been O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction…” “[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted) (Claim was directed to a novolac color developer. The process of making the developer was allowed. The difference between the inventive process and the prior art was the addition of metal oxide and carboxylic acid as separate ingredients instead of adding the more expensive pre-reacted metal carboxylate. The product-by-process claim was rejected because the end product, in

both the prior art and the allowed process, ends up containing metal carboxylate. The fact that the metal carboxylate is not directly added, but is instead produced in-situ does not change the end product.). See MPEP 2113.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 1, 43, 49, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in view of Weitz et al. (US Patent 6,075,013, issued 13 Jun 2000, of record).

Naggi et al. discloses as above.

Naggi et al. does not disclose the specific composition further comprising a non-heparin anticoagulant.

Weitz et al. teaches the use of modified low molecular weight heparin (column 10, lines 25-30) obtained by oxidation (column 10, lines 47-53) used in conjunction with conventional thrombolytic treatments, such as tissue plasminogen activator, an anti-tissue factor compound (column 11, lines 20-30).

It would have been obvious to one of ordinary skill at the time of the invention to combine depolymerized and supersulfated heparin disclosed by Naggi et al. in conjunction with conventional thrombolytic treatments, such as tissue plasminogen

activator, an anti-tissue factor compound, as taught by Weitz et al. Both inventions are drawn to antithrombotic compositions. See MPEP 2144.06, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art."

Amended claims 1 and 56-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, of record).

Naggi et al. discloses as above.

Naggi et al. does not specifically disclose a polymeric structure comprising an oxidized heparin fraction, wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or copolymerization, non-covalently incorporated into a matrix of the polymeric structure, or encapsulated as a biomedical material within the polymeric structure, or wherein said biocompatible polymer is ethylene vinyl acetate.

Conrad et al. teaches size separated fractions of depolymerized low molecular weight heparin produced by periodate oxidation (column 3, lines 25-29) that are non-anticoagulant and show antiproliferative activity with respect to smooth muscle cells (abstract), or an angiogenesis inhibition characteristic. Conrad et al. teaches the size separated fractions are treated chemically to produce O-oversulfation to increase

activity (column 4, lines 27-37). Conrad et al. teaches the heparin administered in the form of an implant containing biodegradable polymer materials such as collagen, formulated as patches or beads, which is encapsulation as a biomedical material, or by local administration through a continuous release device such as a supporting matrix, which is understood to be non-covalent incorporation into the matrix (column 10, lines 47-50 and 60-63). Conrad et al. teaches the use of the specific polymer ethylene vinyl acetate as the supporting matrix (column 14, lines 34-38).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the depolymerized and supersulfated heparin disclosed by Naggi et al. with the O-oversulfated low molecular weight heparin incorporated into a polymeric structure as taught by Conrad et al. Conrad et al. teaches the size separated fractions are treated chemical to produce O-oversulfation to increase activity (column 4, lines 27-37). Naggi et al. recites "It is also generally recognized that at the same degree of polymerization, the biological activity of polysaccharides increases with their sulfation degree," (column 3, lines 42-44). Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to use of a known technique of supersulfation to improve similar depolymerized low molecular weight heparin in the same way by combining the depolymerized and supersulfated heparin disclosed by Naggi et al. with the O-oversulfated low molecular weight heparin incorporated into a polymeric structure as taught by Conrad et al.

Amended claims 1, 43 and 51-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in view of Conrad et al. (US Patent 5,280,016, issued 18 Jan 1994, of record) as applied to claims 1 and 56-59 above, and further in view of Kerbel et al. (Cancer and Metastasis Reviews, 2001, 20, p79-86, of record).

Naggi et al. in view of Conrad et al. discloses as above. Conrad et al. makes explicit that the antiproliferative activity with respect to smooth muscle cells, or angiogenesis inhibition characteristic, inherent in the compound disclosed by Naggi et al. was recognized in the prior art.

Naggi et al. in view of Conrad et al. does not disclose the specific composition further comprising a non-heparin angiogenic inhibitor, or a cytotoxic or chemotherapeutic agent.

Kerbel et al. teaches the use of combinations of angiogenesis inhibitors (page 82, right column, lines 9-11), such as chemotherapy drugs such as microtubule agents and anti-angiogenic drugs (page 82, right column, lines 14-17). Kerbel et al. teaches the use of combinations of specific drugs such as DC101 antibody to VEGF (vascular endothelial growth factor) receptor-2 (page 83, spanning left column line 23 and right column lines 1-2); thalidomide, interferon alpha, and low molecular weight heparin (page 83, right column, lines 18-22) and angiostatin, endostatin, and interleukin-12 (page 84, left column, lines 1-3).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the depolymerized and supersulfated heparin taught by Naggi et

al. in view of Conrad et al. with the combinations of angiogenesis inhibitors taught by Kerbel et al. See MPEP 2144.06, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." Kerbel et al. teaches the use of low molecular weight heparin in said combinations. One of ordinary skill in the art would be motivated to combine the specific depolymerized and supersulfated heparin taught by Naggi et al. in view of Conrad et al. with the combinations of angiogenesis inhibitors taught by Kerbel et al. because Naggi et al. recites “It is also generally recognized that at the same degree of polymerization, the biological activity of polysaccharides increases with their sulfation degree,” (column 3, lines 42-44).

Amended claims 1, 56, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) in view of Scholander (US Patent 6,461,665, issued 08 Oct 2002, of record).

Naggi et al. discloses as above.

Naggi et al. does not disclose the polymeric structure wherein said oxidized heparin fraction is covalently attached to the polymeric structure by surface grafting or by copolymerization.

Scholander teaches a surface modified to have improved antithrombogenic activity by attaching heparin to the surface to be modified (abstract), comprising reacting

heparin with the surface (column 4, lines 25-40), or surface grafting, or by reacting the heparin with a polymer layer and reacting the heparin-containing polymer with other polymers (column 5, lines 1-30), such as when the heparin is reacted with the later from step (a). The reaction of a heparin-containing polymer with other polymers can be interpreted as copolymerization.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the depolymerized and supersulfated heparin disclosed by Naggi et al. with the surface modified to have improved antithrombogenic activity by attaching heparin to the surface to be modified taught by Scholander. One of ordinary skill in the art would be motivated to combine the specific depolymerized and supersulfated heparin disclosed by Naggi et al. with the surface modified to have improved antithrombogenic activity taught by Scholander because Naggi et al. recites "It is also generally recognized that at the same degree of polymerization, the biological activity of polysaccharides increases with their sulfation degree," (column 3, lines 42-44).

(10) Response to Argument

Appellant's arguments with respect to the above grounds of rejection focus on rejection of claims 1, 2, 5, 6, 43, 91-94 under 35 U.S.C. 102(b) as being anticipated by Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record).

Appellant contends that Naggi does not teach or disclose each and every feature of claim 1. Appellant again cites Lundin, Journal of Biological Chemistry, vol. 275, no. 32, (August 11, 2000) as providing evidence that it is known in the art that desulfation

results in inhibition of FGF-2 induced angiogenesis. However, Naggi discloses that the invention of Naggi is drawn to a depolymerized heparin that possesses a sulfation degree at least 20% higher than that of starting heparin (column 5, lines 5-10). As noted by Appellant, Naggi does not teach or provide evidence that the compound disclosed by Naggi possess the characteristic of inhibiting of FGF-2 induced angiogenesis. However, this is deemed to be an inherent property of the chemical disclosed by Naggi, meeting the structural limitations of the instant invention as claimed.

As recited in the body of the rejection above, the compound disclosed by Naggi meets the structural limitations of the invention as claimed. Appellant asserts that the structure disclosed by Naggi does not meet the structural limitations of the invention as claimed by reemphasizing the language of the claim, however these limitations are met by the structure disclosed by Naggi even though Naggi does not use the exact language found in the instant claim. The product-by-process is described by the process of having been "O-sulfated by sulfate substitution at oxygen bonds within repeating units of the first oxidized heparin fraction", and said process would make the structure disclosed by Naggi. It is noted that the instant specification discloses oxidation of heparin fractions using **any** oxidizing agent **without limitation**, including reagents such as peroxide and O_2 (instant specification, page 8, paragraph 26). Naggi uses chlorosulfonic acid, a strong oxidizing agent, to depolymerize the heparin and teaches the prior art uses peroxides to depolymerize heparin (column 4, lines 45-55). While the specification suggests the oxidation converts hydroxyl residues to aldehydes and acids and provides embodiments wherein a defined percent of the hydroxyl residues are

oxidized (instant specification, page 8, paragraph 26), **no structural limitation regarding percent of the hydroxyl residues oxidized is recited in the invention as claimed**. 3Therefore the invention as recited in the instant claims encompasses the compound disclosed by Naggi wherein the heparin is oxidized to depolymerize the heparin.

The instant specification does not disclose different structural features responsible for claimed properties such as said first anticoagulant reduction characteristic and said second anticoagulant reduction characteristic, or for fully inhibiting fibroblast growth factor (FGF2) induced angiogenesis. As recited above the compound disclosed by Naggi meets the structural limitations of the invention as claimed and exhibits said second anticoagulant reduction characteristic, therefore there is a reasonable expectation based on what is disclosed that other characteristics of said compound are necessarily present, see MPEP 2112.01 II, “A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Appellant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)".

Appellant contends that Naggi does not disclose the features of claim 93, specifically wherein

> “the anticoagulant reduction characteristic comprises a first anticoagulant reduction characteristic, a second anticoagulant reduction characteristic, or a combination thereof;
> wherein the first anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a mean percent inhibition of platelet clot strength by factor of at least about 8 relative to a mean percent inhibition of platelet clot strength of unfractionated heparin under a condition of the concentration of

the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood;

wherein the second anticoagulant reduction characteristic is that the oxidized heparin fraction reduces a prolongation of clotting time of human blood by at least 75% relative to a prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT); and

wherein the angiogenesis inhibition characteristic is that the oxidized heparin fraction in an endothelial cell (EC) growth medium cancels an effect of recombinant human fibroblast growth factor (FGF2) on EC tube formation in the EC growth medium under a condition of the concentration of FGF2 in the EC growth medium being sufficient to increase a length or area of the EC tube formation by a factor of at least about 2 if the oxidized heparin fraction is not in the EC growth medium."

Appellant notes that the data in the APTT column of TABLE 1 of Naggi at col. 9, lines 50-59 is not expressed in units of clotting time or prolongation of clotting time, but rather is expressed in units of U/mL. Examiner has cited as evidence definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service to show that determination of levels of anticoagulation are ***known in the art to be acceptably measured in terms of units/mL, or U/mL,*** (Heparin Antifactor Xa Assay, page 2, sections **Reference Interval** and **Use**) ***in addition to units of time***. The definition of Activated Partial Thromboplastin Time from Massachusetts General Hospital Pathology Service shows the Heparin Antifactor Xa Assay is an equivalent assay to the measurement of Activated Partial Thromboplastin Time (Activated Partial Thromboplastin Time, parage 2, section

Limitations.) The depolymerized and supersulfated heparin disclosed by Naggi et al. shows a reduction of the APTT or Anti-Xa as measured in terms of units/mL in table I (column 9, lines 50-65) for products AH-17 and AH-19, relative to the heparin D-212, the reduction being approximately 76.5% (0.05 U/ml / 0.212 U/ml) for the same dose (50 IU/kg), or a ***reduced prolongation of clotting time*** of human blood by at least 75% relative to the prolongation of clotting time of human blood by unfractionated heparin under a condition of the concentration of the oxidized heparin fraction in human blood being equal to the concentration of the unfractionated heparin in human blood, subject to the clotting time being a prothrombin time (PT) or an activated partial thromboplastin time (APTT). The values disclosed by Naggi, expressed in units of U/mL and not units of time, would be understood to be a measure of clotting time or prolongation of clotting time based on the understanding in the art as provided by the evidence of evidence definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service.

With regard to claim 2 and 6, the instant specification does not disclose different structural features responsible for claimed properties such as first anticoagulant reduction characteristic and a second anticoagulant reduction characteristic. As recited above with regard to claim 93, the compound disclosed by Naggi exhibits said second characteristic, therefore there is a reasonable expectation based on what is disclosed that other characteristics of said compound are necessarily present, see MPEP 2112.01 II, “A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties Appellant discloses and/or

claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990)".

With regard to claim 5, the APTT values disclosed by Naggi, expressed in units of U/mL and not units of time, would be understood to be a measure of clotting time or prolongation of clotting time based on the understanding in the art as provided by the evidence of evidence definitions of Activated Partial Thromboplastin Time and Heparin Antifactor Xa Assay from Massachusetts General Hospital Pathology Service, as discussed above regarding claim 93.

With regard to claim 91, Appellants assert that 2.6:1 is not about 5:1, as 5:1 is more than 90% higher than 2.6:1. It is clear that 2.6:1 is not 5:1. However, are recited in the body of the rejection above, "The term "sulfate to carboxylate ratio of about 5:1" in instant claim 91 broadens the ratio without guidance as to the range encompassed by the term "about", and the disclosed sulfation degree of 2.6, or ratio of sulfate to carboxylate of 2.6:1, is interpreted to be about 5:1 because it is the same order of magnitude." Appellants provide no guidance as to metes and bounds of the term "about" in the context of the instant invention, therefore it is maintained that 2.6:1 is **about** 5:1 within the context of the instant invention.

With regard to claim 92, as recited in the body of the rejection above "Naggi et al. discloses a preferred embodiment of depolymerized and supersulfated heparin wherein the molecular weight is 3000-5000 and the sulfation degree is 2.6 (example 12 at column 12, lines 1-30), or a heparin fraction wherein 52% of the primary and secondary hydroxyl groups are substituted by O-sulfate esters…" This embodiment has 52%

hydroxyl groups substituted by O-sulfate esters, meeting the limitation of instant claim 92.

With regard to claim 94, Examiner has cited Naggi at column 4, lines 10-20 and column 5, lines 5-30 to support the chemical reaction implicit in example 12 at column 12, lines 1-30 within Naggi. Therefore Naggi provides evidence that the chemical reaction occurs as described by the Examiner, and the process disclosed by Naggi implicitly anticipates claim 94.

With regard to claim 43, the disclosure of Naggi at column 10, lines 55-57 recites the pharmaceutical composition containing the depolymerized and supersulfated heparin of Naggi. As recited in the body of the rejection above, this composition as stated containing said heparin of Naggi is about 100% of said heparin of Naggi. Appellant has not provided evidence that Naggi requires said pharmaceutical composition to contain other than 100% of said heparin of Naggi. Therefore this disclosure by Naggi anticipates claim 43.

Appellant's arguments with regard further grounds of rejection reiterate the remarks with regard to Naggi et al. (US Patent 4,727,063, issued 23 Feb 1988, of record) and are addressed as above.

For these reasons, the rejections are deemed proper and maintained.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Jonathan Lau/

Patent Examiner

Art Unit 1623

Conferees:

/Leigh C. Maier/

Primary Examiner, Art Unit 1623

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Supervisory Patent Examiner, Art Unit 1623